DETAILED ACTION

During the interview dated 11/08/10, it was indicated that the Restriction Requirement mailed 07/20/10 would be withdrawn. Hence, this Office Action:

Election/Restrictions

The Restriction Requirement mailed 07/20/10 is hereby withdrawn.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 06/02/10 has been entered.

Request for Correction of Inventorship

In view of the papers filed 07/13/09, it has been found that this nonprovisional application, as filed, through error and without deceptive intent, improperly set forth the inventorship, and accordingly, this application has been corrected in compliance with 37 CFR 1.48(a). The inventorship of this application has been changed by the addition of Rajeev A. Jain, Jon Swanson, Robert Hontz, John G. Devane, Kenneth Ian Cumming,

Maurice Joseph Anthony Clancy, Janet Elizabeth Codd, and Gary G. Liversidge to the inventorship of the present application.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of Office records to reflect the inventorship as corrected.

Claim Rejections - 35 USC § 103

Claims 1-15, 17-24, 40-75 and 87-90 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bosch et al. US 5,510,118, in view of Stamm et al. WO 98/31360 A1.

Bosch teaches a nanoparticulate therapeutic composition comprising of 99.9-10% by weight of a crystalline drug substance, and from about 0.1 to about 90% by weight of a non-crosslinked surface modifier adsorbed on the surface of the drug substance. See Abstract; and claim 1. The nanoparticulate has an effective average particle size of less than about 400 nm (abstract; column 6, lines 36-54; and claim 1). Suitable drug substance includes anti-diabetic agents (column 5, line 5). The claimed surface modifiers are disclosed in column 5, lines 45 through column 6, lines 1-5. Surface modifier can be used in combination of two or more (column 6, lines 10-12). Bosch further teaches a method for preparing the dispersible particle comprising dispersing a drug substance in a liquid dispersion that contains surface modifier to form a premix, homogenizing the premix, and subjecting the premix to grinding media (columns 7-8; examples; and claims). The obtained dispersion of surface modified drug

nanoparticles is combined with pharmaceutical excipient to form pharmaceutical formulation for oral, rectal, injection administration, and the like (column 8, lines 40 through column 9, lines 1-17). Bosch further teaches that the surface modifier is essentially free of intermolecular crosslinkages (column 6, lines 34-35).

Bosh does not explicitly teach the claimed active, such as glipizide.

Stamm teaches a composition having high bioavailability comprising micronized glipizide as active agent suspended in a solution containing surfactant (page 5, lines 32-38; examples 1 and 6). Stamm further teaches active agent in micronized form having particle size below 20 µm. Thus, it would have been obvious to one of ordinary skill in the art to select glipizide as an active agent because Stamm teaches that glipizide is a well known insoluble drug, and that the need to improve dissolution and bioavailability of glipizide is well known in the art, and because Bosh teaches a formulation suitable for improving bioavailability of a wide variety of active agents including anti-diabetic agents.

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bosch et al., in view of Stamm et al. and Baralle et al. GB 2316316.

Bosch is relied upon for the reasons stated above. The references do not teach the second population of particle having different particle distribution from the particle distribution of (a). However, bimodal particle distribution is known in pharmaceutical art. Baralle teaches a liquid composition comprising bimodal particle size distribution suitable for parenteral administration (abstract; page 3, lines 23-32; and page 7, lines 3 through page 8, lines 1-23). Accordingly, depending in the release profile desired, the

skilled artisan would have been motivated to modify the formulation of Bosch to include a bimodal particle distribution in view of the teachings of Baralle. This is because Baralle teaches a bimodal particle distribution is known in pharmaceutical art, because Baralle teaches a bimodal particle distribution that exhibits a useful sustained release profile that is free of serious side-effects (pages 3-4).

Claims 36-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bosch et al., in view of Stamm et al. and Lo et al. 4,389,397.

Bosch is relied upon for the reason stated above. The references do not explicitly teach the viscosity of the liquid dosage form.

Lo teaches a low water solubility drug is preferably formulated in liquid dosage form having low viscosity to achieve excellent stability and syringability (abstract; and column 4, lines 10-17). Thus, it would have been obvious to one of ordinary skill in the art to prepare a low viscous liquid dosage form in view of the teachings of Bosch and Lo to obtain a stable liquid dosage form suitable for water-insoluble drug. This is because Lo teaches Lo teaches liquid dosage form having high viscosity will cause precipitation, irritation and tissue damage at the injection site (column 1, lines 25-29), because Lo teaches a low viscosity liquid dosage form overcomes the disadvantages in the prior arts and exhibits excellent syringability (ID).

Response to Arguments

Applicant's arguments filed 06/02/10 have been fully considered but they are not persuasive.

Applicant argues that In contrast, the active agent of Desai's composition is "encased in a polymeric shell" and the composition is "prepared without the use of conventional surfactant." Desai, column 1, lines 25-30. Desai further discloses that "[t]he polymeric shell is a crosslinked biocompatible polymer" (column 6, lines 4-5) and that "the polymer *(e.g.,* a protein) may be crosslinked as a result of exposure to high shear conditions in a high pressure homogenizer" (column 8, lines 35- 37). More specifically, Desai describes that the protein surface stabilizer is cross-linked via disulfide bond (column 8, lines 54-56). As such, Desai teaches *away* from the claimed nanoparticulate glipizide composition which comprises a surface stabilizer free of intermolecular cross-linkages and encompassing conventional surfactants.
Stamm is cited for the alleged teaching of selecting glipizide as an active agent and using glipizide in microparticulate form. However, Stamm fails to compensate for the deficiencies of Desai, i.e., even if one skilled in the art would have selected glipizide as the active agent to obtain a composition described by Desai, such composition would be distinguishable from Applicants' claimed invention, as discussed above.

This 103(a) rejection over Desai in view of Stamm has been withdrawn in view of Applicant’s Remarks.

Applicant argues that the combined teachings of Liversidge and Stamm fail to render Applicants' claimed invention obvious because one skilled in the art would not have had any reason to select the active agent of the claimed invention, glipizide, and because a reasonable expectation of successfully obtaining a stable nanoparticulate glipizide composition is lacking. Liversidge, disclose a laundry list of over 40 categories of drugs without any teaching or suggestion of selecting an anti-diabetic agent, such as glipizide, as the active agent. Rather, Liversidge teaches anti-cancer drugs and steroids in preferred embodiments. Similarly, Stamm lists numerous poorly soluble active agents without any explicit teaching to select glipizide. Accordingly, even when the cited references are combined, one skilled in the art would not have gleaned from the cited art that glipizide is a desirable active agent for the nanoparticulate composition.

However, in response to Applicant's arguments, the Examiner notes that Bosch, similar to Liversidge teaches a pharmaceutical delivery system useful for improving bioavailability of poorly water soluble drugs. Columns 1-2. A useful delivery system that any drug substances which could not have been administered orally due to poor bioavailability may be effectively administered in accordance with the invention (ID). This delivery system is suitable for a wide variety of active agents such as antidiabetic agents (column 5, line 5). Accordingly, one of ordinary skill in the art would have been motivated to optimize the delivery system of Bosch for any desired poorly water soluble drug with the expectation of at least similar results. The secondary reference, Stamm et

al., recognizes that glipizide is poorly soluble in water, and therefore, low in bioavailability. See for example, pages 1 and 3.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to S. Tran whose telephone number is (571) 272-0606. The examiner can normally be reached on M-F 8:30 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax can be reached on (571) 272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. Tran/
Primary Examiner, Art Unit 1615